EXHIBIT 23

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Increased Risk of Stroke Associated With Nonsteroidal Anti-Inflammatory Drugs: A Nationwide Case–Crossover Study

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Increased Risk of Stroke Associated With Nonsteroidal Anti-Inflammatory Drugs

A Nationwide Case–Crossover Study

Chia-Hsuin Chang, MD, ScD; Wen-Yi Shau, MD, PhD; Chuei-Wen Kuo, PharmD, MSc; Shu-Ting Chen, BA; Mei-Shu Lai, MD, PhD

Background and Purpose—Limited studies assessed cerebrovascular safety of individual nonsteroidal anti-inflammatory drugs (NSAIDs). We evaluated the risk of ischemic and hemorrhagic stroke associated with short-term use of selective and nonselective NSAIDs in a Chinese population with a high incidence of stroke.

Methods—A retrospective case–crossover study was conducted by analyzing the Taiwan National Health Insurance Database. We identified all ischemic and hemorrhagic stroke patients in 2006, aged ≥20 years, based on International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes from inpatient claims and defined the index date as the date of hospitalization. For each patient, we defined case period as 1 to 30 days before the index date and control period as 91 to 120 days before the index date. A pharmacy prescription database was searched for NSAID use during the case and control periods. We calculated adjusted ORs and their 95% CIs with a conditional logistic regression model.

Results—A total of 28 424 patients with ischemic stroke and 9456 patients with hemorrhagic stroke were included. For ischemic stroke, a modest increased risk was evident for all oral NSAIDs with adjusted ORs (95% CI) ranging from1.20 (1.00 to 1.44) for celecoxib to 1.90 (1.39 to 2.60) for ketorolac. For hemorrhagic stroke, oral ketorolac was associated with a significantly higher risk with OR of 2.69 (1.56 to 4.66). Significantly increased risk was found for parenteral NSAIDs, in particular ketorolac, with an OR of 3.92 (3.25 to 4.72) for ischemic stroke and 5.98 (4.40 to 8.13) for hemorrhagic stroke.

Conclusions—Use of selective and nonselective NSAIDs was associated with an increased risk of both ischemic and hemorrhagic stroke, strikingly high for parenteral ketorolac. **(*Stroke*. 2010;41:1884-1890.)**

Key Words: acute stroke ■ cerebral infarct ■ cerebrovascular disease ■ intracerebral hemorrhage ■ nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medication worldwide, and their safety needs to be scrutinized. Several studies suggest cyclo-oxygenase-2 enzyme (COX-2) selective NSAIDs or coxibs are associated with an increased risk of cardiovascular adverse outcome, particularly acute myocardial infarction.[1–3] There is also uncertainty regarding the safety of COX-2 nonselective NSAIDs.[4] In a recently published placebo-controlled trial, the nonselective NSAID naproxen was also associated with an increased cardiovascular risk.[5] This raises the concern that cardiovascular toxicities were recognized as a possible class effect of all NSAIDs and not just coxibs.

However, few studies specifically evaluated the cerebral vascular safety of NSAIDs, including risk of acute ischemic and hemorrhagic stroke. Two studies found that rofecoxib, etoricoxib, and valdecoxib were associated with significant risk of ischemic stroke.[6,7] In a prospective cohort study, researchers observed a greater risk for celecoxib, although not statistically significant.[8] Nonselective NSAIDs, including naproxen, diclofenac, and ibuprofen, might be associated with an increased risk of ischemic stroke.[6,8,9] Conflicting results are noted in studies investigating the outcome of hemorrhagic stroke[10–14] We examined the risk of ischemic and hemorrhagic stroke associated with short-term use of selective and nonselective NSAIDs in a Chinese population with a high incidence of stroke.

Subjects and Methods

The protocol of this study was approved by the National Taiwan University Hospital Research Ethics Committee. We used the case–

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From the Department of Internal Medicine (C.-H.C.), National Taiwan University Hospital, Taipei, Taiwan; the Institute of Preventive Medicine (C.-H.C., M.-S.L.), College of Public Health, National Taiwan University, Taipei, Taiwan; the Division of Health Technology Assessment (W.-Y.S.), Center for Drug Evaluation, Taipei, Taiwan; the National Health Insurance Mediation Committee (C.-W.K.), Department of Health, Executive Yuan, Taipei, Taiwan; and the Statistics Office (S.-T.C.), Department of Health Executive Yuan, Taipei, Taiwan.

Correspondence to Mei-Shu Lai, College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei, Taiwan 10020. E-mail mslai@ntu.edu.tw

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crossover study design to assess the relationship between NSAID use and risk of stroke. Instead of using matched control subjects, the past experience of the case served as the case's own control. Therefore, stable confounders, including those that cannot be measured, be poorly measured, or are unknown, cancel each other out.[15,16] The case–crossover design has been widely used as a tool to evaluate drug safety and is particularly suitable when the exposure is intermittent, the effect on risk is immediate and transient, and the outcome is abrupt. The available reports suggested that the potential NSAID-related cerebrovascular toxicity would be immediate and transient and that the outcome would be abrupt such that the case–crossover design is an appropriate method in this setting.[17]

Data Source

The Taiwan National Health Insurance Database includes complete outpatient visits, hospital admissions, prescriptions, disease, and vital status for 99% of the 23 million population in Taiwan.[18] We established the longitudinal medical history of each beneficiary by linking several computerized administrative, claims data sets, and National Death Registry through the civil identification number unique to each beneficiary and date of birth. Our source population comprised all beneficiaries aged ≥20 years with continuous coverage from January 1, 2005, to December 31, 2006.

Study Population

Our study populations were patients with ischemic stroke and hemorrhagic stroke (including subarachnoid hemorrhage and intracerebral hemorrhage) that led to hospitalization. Stroke of lesser severity that did not result in hospitalization, occlusion, and stenosis of carotid, vertebral, and cerebral arteries but without cerebral infarction, and transient cerebral ischemia were not studied. From the source population, we identified patients with any hospitalized event of ischemic stroke (defined by having an International Classification of Diseases, 9th Revision, Clinical Modification code of 433, 434, 436) and hemorrhagic stroke (code 430, 431, 432) as principle discharge diagnoses. For those who had ≥2 hospitalizations for stroke in 2006, only the first event was included. Date of hospitalization was defined as the index date. Patients who had prior hospital admission or outpatient visits in 2005 with a diagnosis code of stroke were not included. We excluded patients who had concomitant diagnoses of trauma (code 800 to 804, 850 to 854, V57), diagnoses of acute myocardial infarction (code 410), and acute ischemic and hemorrhagic stroke during the same hospitalization in 2006 to reduce the likelihood of misdiagnoses of head injury or stroke of uncertain entity. We also excluded patients who were admitted for any reason during 120 days before the index date due to dosage and duration of NSAID use in hospitalization was difficult to ascertain.

Data on Drug Exposure and Confounding Factors

NSAIDs have been reimbursed by the Taiwan National Health Insurance since its launch in 1996. The estimated total NSAID prescriptions were 14 045 defined daily dose (DDD)/1000 inhabitant/year, accounting for 3.3% of the annual total drug expenditure. The main exposures of interest in this study were most commonly used selective and nonselective NSAIDs in Taiwan in 2005 to 2006 that included celecoxib (the only coxib that was on the market), indomethacin, sulindac, diclofenac, ketorolac, piroxicam, meloxicam, ibuprofen, naproxen, ketoprofen, and mefenamic acid based on the drug use 95% profile. We collected information of type of drug prescribed (according to the anatomic therapeutic chemical classification system), dosage, route of administration (oral, parenteral), date of prescription, days supply, and total number of drug pills dispensed from the pharmacy prescription database. We determined mean daily dose by multiplying the number of pills dispensed by the dose prescribed divided by the recorded days' supply. Data were presented as the number of DDD, which was established by an expert panel as the typical maintenance dose required when the drug is used for its main indication in an adult.[19] Other concomitant drug use included antihypertensive agents (anatomic therapeutic chemical code C02), statins (C10AA), insulin (A10A), sulfonylurea (A10BB), thiazolidinediones (A10BG), glinides (A10BX02, A10BX03), β-blockers (C07), angiotensin-converting enzyme inhibitors (C09AA) or angiotensin receptor blockers (C09CA), calcium channel blockers (C08), loop diuretics (C03C), vitamin K antagonists (B01AA), nonaspirin antiplatelet agents (B01AC except B01AC06), and low-dose aspirin (B01AC06). We also collected information on patient's age, gender, comorbidities, including ischemic heart disease, diabetes mellitus, hypertension, atrial fibrillation, congestive heart failure, chronic renal disease, chronic liver disease, chronic lung disease, peptic ulcer disease, rheumatoid arthritis, osteoarthritis, migraine, and cancer based on International Classification of Diseases, 9th Revision, Clinical Modification codes (Supplemental Table I; available at http://stroke.ahajournals.org).

Statistical Analysis

We calculated the gender and age distribution for all cases in 2006. For each patient, we defined case period as 1 to 30 days before the index date and the control period as 91 to 120 days before the index date. This definition of case and control periods was used in prior studies based on pharmacological properties of NSAIDs.[20,21] The proportion of patients with comorbidities between the case period and the control period was compared by the McNemar's test. Persons were considered current users of an NSAID during the start date and end date of a prescription.

We compared NSAID use between case and control periods and calculated crude ORs and their 95% CIs for current use of selective NSAID, nonselective NSAID overall, and individual NSAID with nonuse as the reference group by conditional logistic regression. Separate analyses were conducted for use of oral and parenteral NSAIDs. To evaluate a possible frequency–response relation, we estimated the mean daily dosage of NSAID use during the case and control periods among users and classified them as regular (≥0.5 DDD/day) or intermittent (<0.5 DDD/day) users in the analysis and calculated risk estimates for different frequency of use. In the multivariable analysis, we calculated adjusted OR simultaneously controlled for use of either selective or nonselective NSAIDs as well as all other potential time-varying confounding variables, including discordant use of antihypertensive agents, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, calcium channel blockers, statins, insulin, sulfonylurea, thiazolidinediones, and aspirin between case and control periods. In the sensitivity analysis, we excluded the recent 7 days of drug exposure and used different control periods of 31 to 60 and 61 to 90 days before the index date to see whether results would change substantially.

Furthermore, stratified analysis was performed to evaluate potential effect modification. The cases were separated according to (1) regular aspirin use (defined as use of any dose of aspirin for ≥28 days during 1 to 150 days before the index date); (2) hypertension; (3) diabetes; and (4) previous cardio- or cerebrovascular disease. A likelihood ratio test was used to compare the full model with the interaction terms against the model without interaction terms to test whether the risk is modified by these characteristics. A 2-sided probability value <0.05 was considered to be statistically significant.

Results

We identified 47 634 patients aged ≥20 years hospitalized for acute ischemic or hemorrhagic stroke in 2006. After excluding those who did not meet our study entry criteria, a total of 28 424 patients with ischemic stroke (54% male, mean age 68.8 years) and 9456 patients with hemorrhagic stroke (58% male, mean age 62.7 years) were included in the final analysis (Figure). Among them, 80% of patients with ischemic stroke and 76% of patients with hemorrhagic stroke received brain imaging study during their hospitalization. Table 1 summarized the proportion of patients with comorbidities during the case period (1 to 30 days before index hospitalization) and control period (91 to 120 days before

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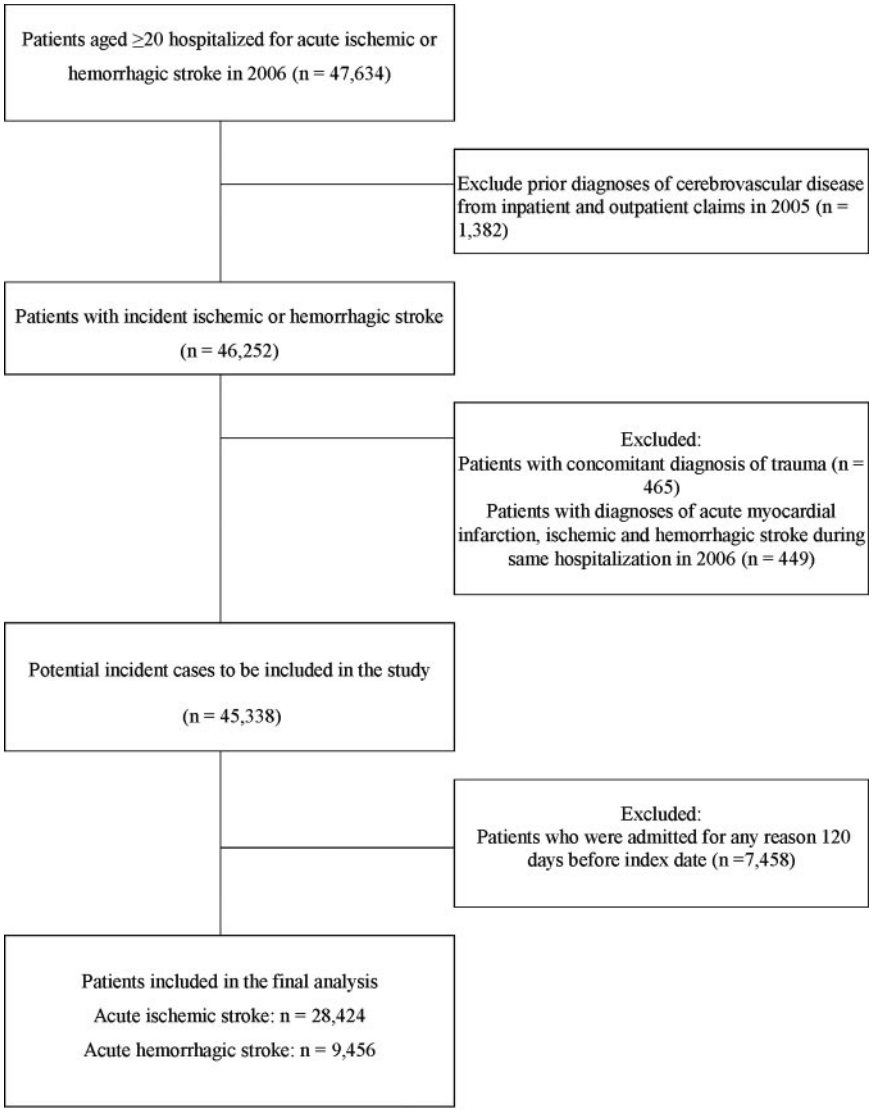

Figure. Flow of the study cohort.

index hospitalization). As compared with the control period, a significantly higher proportion of patients had a diagnosis of hypertension during the case period (39.5% versus 45.2% for patients with ischemic stroke; 32.2% versus 36.6% for patients with hemorrhagic stroke, respectively), although the differences were all significant for other comorbidities because of the large number of patients included in our study.

Supplemental Tables II and III summarize use patterns of oral and parenteral NSAIDs 120 days before index hospitalization among patients with acute stroke in Taiwan. As compared with other oral NSAIDs, celecoxib, meloxicam, and sulindac were prescribed with longer days' supplies, whereas piroxicam and naproxen were prescribed at a higher mean daily dosage. Ketorolac, ketoprofen, and diclofenac were the commonly used parenteral NSAIDs. The majority received NSAIDs due to acute pain such as musculoskeletal injuries and renal colic, whereas only 6% were due to headache. Approximately one third of them were new users without any NSAID prescription 180 days before the study period. Table 1 also summarizes use of selective and nonselective NSAIDs as well as concomitant medications during the case period and the control period. A significantly higher proportion of patients used nonselective NSAIDs in the case period as compared with in the control period. Meanwhile, significantly more patients also took angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and calcium channel blockers during the case period.

Table 2 presents crude and adjusted ORs and their 95% CIs for individual oral NSAIDs by conditional logistic regression. We found no substantial change after controlling for other potential time-varying confounding variables in the multivariable analysis. For ischemic stroke, a modest increased risk was evident for all oral NSAIDs. The adjusted ORs (95% CI) ranged from1.20 (1.00 to 1.44) for celecoxib to 1.90 (1.39 to 2.60) for ketorolac. There were sufficient numbers of regular ($\geq$0.5 DDD/day) and intermittent ($<$0.5 DDD/day) users of diclofenac, ibuprofen, and mefenamic acid that allowed us to conduct frequency–response analysis. Risks were similar for regular and intermittent users of these NSAIDs. For acute hemorrhagic stroke, results were similar, although the strength of association seemed to be even higher for some of

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Table 1. Comorbidities and Concomitant Medication During 1 to 30 Days and 91 to 120 Days Before Incident Hospitalization for Ischemic and Hemorrhagic Stroke

	Ischemic Stroke (N=28 424)		Hemorrhagic Stroke (N=9456)	
	Case Period (1–30 Days Before Index Day; %)	Control Period (91–120 Days Before Index Day; %)	Case Period (1–30 Days Before Index Day; %)	Control Period (91–120 Days Before Index Day; %)
Comorbidity, %				
Diabetes mellitus	24.2	22.4	20.2	18.6
Hypertension	45.2	39.5	36.6	32.2
Atrial fibrillation	2.0	1.8	1.6	1.5
Congestive heart failure	4.2	3.5	3.6	3.1
Chronic renal disease	3.0	2.8	2.6	2.2
Chronic liver disease	3.0	2.9	2.5	2.4
Chronic lung disease	6.7	6.4	5.8	5.5
Peptic ulcer disease	8.3	7.5	6.9	6.4
Osteoarthritis	8.9	8.0	7.6	6.8
Rheumatoid arthritis	0.6	0.6	0.6	0.6
Migraine	0.5	0.3	0.5	0.4
Cancer	0.1	0.1	0.2	0.2
Concomitant medication, %				
Statins	8.5	7.4	4.3	3.9
Insulin	3.8	2.6	1.7	1.4
Sulfonylurea	18.0	16.7	6.7	6.7
Thiazolidinediones	2.6	2.4	0.8	0.8
Glinides	1.7	1.5	0.9	0.9
Antihypertensive agents	6.2	4.9	4.0	3.5
ACE inhibitors or ARBs	24.0	20.0	13.9	12.5
β-blockers	21.0	16.0	14.8	10.6
Calcium channel blockers	31.0	24.3	18.8	15.9
Loop diuretics	1.2	1.0	0.9	0.8
Vitamin K antagonists	1.3	1.1	1.1	1.0
Nonaspirin antiplatelet agents	0.6	0.6	0.2	0.3
Low-dose aspirin	6.9	6.8	3.5	3.9
Celecoxib	1.7	1.5	1.1	1.0
Nonselective NSAIDs	29.2	21.6	24.6	17.3

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

the studied NSAIDs. Noteworthy, use of oral ketorolac was also associated with a significantly higher risk with OR of 2.69 (1.56 to 4.66). No significantly increased risk of hemorrhagic stroke was found for use of oral celecoxib (OR 1.07; 0.72 to 1.59). Significantly increased risk was found for use of parenteral NSAIDs, in particular ketorolac, with ORs of 3.92 (3.25 to 4.72) for ischemic stroke and 5.98 (4.40 to 8.13) for hemorrhagic stroke (Table 3).

Results were similar in the sensitivity analysis using a different control period of 31 to 60 and 61 to 90 days before the index date. Effects of parenteral nonselective NSAIDs were attenuated but still remained significant after excluding recent 7 days of drug exposure (Table 4).

We found significant effect modification by regular aspirin use for ischemic stroke (probability values for test for interaction 0.04 by the likelihood ratio test). The risk for ischemic stroke associated with oral and parenteral nonselective NSAIDs was reduced but remained significant among regular aspirin users with ORs of 1.55 (1.34 to 1.80) and 2.39 (1.60 to 3.57) as compared with 1.73 (1.65 to 1.83) and 3.23 (2.77 to 3.76) for those not using aspirin regularly. Risk estimates seemed to be uniform among other predefined subgroups, including patients with diabetes, hypertension, or prior cardio- and cerebrovascular diseases.

Discussion

In this study, we analyzed a nationwide health insurance claims database and found an increased risk for ischemic and hemorrhagic stroke was evident for all selective and nonselective NSAIDs, particularly when used parenterally. Risk was highest for ketorolac as compared with other NSAIDs.

Four population-based studies in Denmark, the United Kingdom, the United States, and The Netherlands investigated nonselective NSAIDs, selective COX-2 inhibitors, and

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Table 2. Risk of Ischemic and Hemorrhagic Stroke Associated With Current Use of Oral Selective and Nonselective of NSAIDs

	Ischemic Stroke (N=28 424)				Hemorrhagic Stroke (N=9456)			
Medication	No. of Patients Use During Case Period But Not Control Period	No. of Patients Use During Control Period But Not Case Period	Crude OR (95% CI)	Adjusted OR* (95% CI)	No. of Patients Use During Case Period But Not Control Period	No. of Patients Use During Control Period But Not Case Period	Crude OR (95% CI)	Adjusted OR* (95% CI)
Celecoxib	290	233	1.24 (1.05–1.48)	1.20 (1.00–1.44)	54	50	1.08 (0.74–1.59)	1.07 (0.72–1.59)
Nonselective NSAIDs overall	4727	2593	1.82 (1.74–1.91)	1.71 (1.63–1.80)	1455	767	1.89 (1.73–2.06)	1.80 (1.65–1.97)
Ketorolac	131	63	2.08 (1.54–2.81)	1.90 (1.39–2.60)	48	18	2.66 (1.55–4.58)	2.69 (1.56–4.66)
Ketoprofen	108	63	1.71 (1.25–2.34)	1.71 (1.24–2.35)	31	20	1.55 (0.88–2.72)	1.48 (0.84–2.61)
Diclofenac	2309	1416	1.63 (1.53–1.74)	1.55 (1.45–1.66)	653	421	1.55 (1.37–1.75)	1.50 (1.32–1.69)
≥0.5 DDD/day	2077	1252	1.66 (1.55–1.78)	1.61 (1.50–1.73)	580	378	1.53 (1.35–1.75)	1.49 (1.30–1.69)
<0.5 DDD/day	232	164	1.42 (1.16–1.73)	1.18 (0.96–1.46)	73	43	1.70 (1.17–2.47)	1.60 (1.09–2.35)
Piroxicam	355	237	1.50 (1.27–1.77)	1.50 (1.26–1.78)	81	62	1.31 (0.94–1.82)	1.25 (0.90–1.75)
Naproxen	321	212	1.51 (1.27–1.80)	1.46 (1.22–1.74)	104	51	2.04 (1.46–2.85)	1.97 (1.40–2.77)
Ibuprofen	963	642	1.50 (1.36–1.66)	1.45 (1.31–1.61)	292	178	1.64 (1.36–1.98)	1.54 (1.28–1.86)
≥0.5 DDD/day	823	542	1.52 (1.36–1.69)	1.51 (1.35–1.69)	244	153	1.60 (1.30–1.95)	1.51 (1.23–1.86)
<0.5 DDD/day	140	100	1.40 (1.08–1.81)	1.26 (0.96–1.66)	48	25	1.92 (1.18–3.11)	1.72 (1.06–2.81)
Meloxicam	473	335	1.43 (1.24–1.64)	1.38 (1.20–1.60)	117	75	1.56 (1.17–2.09)	1.48 (1.11–1.99)
Sulindac	299	223	1.34 (1.13–1.60)	1.26 (1.05–1.50)	69	57	1.21 (0.85–1.72)	1.13 (0.79–1.62)
Mefenamic acid	1400	930	1.51 (1.39–1.64)	1.26 (1.05–1.50)	396	243	1.63 (1.39–1.91)	1.13 (1.79–1.62)
≥0.5 DDD/day	1267	853	1.49 (1.36–1.62)	1.43 (1.30–1.56)	354	213	1.66 (1.40–1.97)	1.61 (1.35–1.91)
<0.5 DDD/day	133	77	1.73 (1.31–2.29)	1.51 (1.13–2.02)	42	30	1.40 (0.88–2.24)	1.25 (0.78–2.01)
Indomethacin	203	155	1.31 (1.06–1.61)	1.24 (1.00–1.54)	71	50	1.42 (0.99–2.04)	1.39 (0.96–2.00)

*Conditional logistic regression adjusted for important potential time-varying confounding variables of all discordant use of antihypertensive agents, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, calcium channel blockers, statins, insulin, sulfonylurea, thiazolidinediones, and aspirin between case and control periods.

the risk of ischemic stroke.[6–9] They found the ORs for ischemic stroke ranged from 1.2 to 1.7 for a variety of nonselective NSAIDs, including ibuprofen, indomethacin, diclofenac, and naproxen. A nested case–control study observed an exposure period as short as 14 days was associated with a significantly increased risk of ischemic stroke.[6] In a prospective population-based cohort study, Haag and colleagues found use of any NSAID was related to the risk of hemorrhagic stroke with a hazard ratio of 2.03, albeit nonsignificant.[8] Conflicting results were reported among additional 5 case–controlled studies and 1 retrospective cohort study regarding hemorrhagic stroke as the outcome.[10–14] Although most of them suggested null findings, CIs around risk estimates were so wide that a small but clinically significant increased risk cannot be safely excluded.

The present study findings in general support results from prior observational studies that a greater risk of stroke was not limited to the use of COX-2 inhibitors but also some traditional nonselective NSAIDs. Our study results were consistent with the reports by Haag and colleagues suggesting NSAID use was associated with increased risk of both ischemic and hemorrhagic stroke. We found the hazards for stroke associated with most oral NSAIDs were small with ORs between 1.2 and 1.9 in contrast to >2.6-fold increased risk in hemorrhagic stroke for oral ketorolac. Our frequency–response analysis suggested that the risks might become elevated even for use <15 days. The risks were evident among all subgroups of patients with or without cardiovascular risk factors.

We found use of parenteral NSAID was associated with a substantially high risk for both ischemic and hemorrhagic

Table 3. Risk of Ischemic and Hemorrhagic Stroke Associated With Current Use of Parenteral Selective and Nonselective of NSAIDs

	Ischemic Stroke (N=28 424)				Hemorrhagic Stroke (N=9456)			
Medication	No. of Patients Use During Case Period But Not Control Period	No. of Patients Use During Control Period But Not Case Period	Crude OR (95% CI)	Adjusted OR* (95% CI)	No. of Patients Use During Case Period But Not Control Period	No. of Patients Use During Control Period But Not Case Period	Crude OR (95% CI)	Adjusted OR* (95% CI)
Nonselective NSAIDs overall	898	259	3.47 (3.02–3.98)	3.11 (2.70–3.59)	392	85	4.61 (3.65–5.83)	4.17 (3.29–5.28)
Ketorolac	637	142	4.49 (3.74–5.38)	3.92 (3.25–4.72)	316	48	6.58 (4.86–8.91)	5.98 (4.40–8.13)
Diclofenac	118	38	3.11 (2.15–4.48)	2.88 (1.98–4.21)	40	21	1.91 (1.12–3.23)	1.65 (0.97–2.82)
Ketoprofen	186	99	1.88 (1.47–2.40)	1.81 (1.41–2.33)	69	26	2.65 (1.69–4.16)	2.46 (1.56–3.88)

*Conditional logistic regression adjusted for important potential time-varying confounding variables of all discordant use of antihypertensive agents, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, calcium channel blockers, statins, insulin, sulfonylurea, thiazolidinediones and aspirin between case and control periods.

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Table 4. Risks of Ischemic and Hemorrhagic Stroke Associated With NSAID Use on Different Definition of Control Period

	Ischemic Stroke			Hemorrhagic Stroke		
	Case Period 8–30 Days Before Index Date Control Period 98–120 Days Before Index Date	Case Period 1–30 Days Before Index Date Control Period 31–60 Days Before Index Date	Case Period 1–30 Days Before Index Date Control Period 61–90 Days Before Index Date	Case Period 8–30 Days Before Index Date Control Period 98–120 Days Before Index Date	Case Period 1–30 Days Before Index Date Control Period 31–60 Days Before Index Date	Case Period 1–30 Days Before Index Date Control Period 61–90 Days Before Index Date
Celecoxib	1.07 (0.89–1.28)	1.36 (1.08–1.71)	1.22 (1.00–1.48)	1.06 (0.71–1.60)	1.47 (0.88–2.45)	0.99 (0.67–1.46)
Nonselective NSAID (oral)	1.20 (1.14–1.27)	1.77 (1.68–1.88)	1.73 (1.64–1.82)	1.31 (1.19–1.45)	1.60 (1.45–1.77)	1.65 (1.50–1.81)
Ketorolac (oral)	1.41 (0.71–2.79)	1.48 (1.09–2.00)	1.26 (1.04–1.53)	1.36 (0.96–1.93)	3.32 (1.79–6.16)	3.58 (1.93–6.65)
Nonselective NSAID (parenteral)	1.46 (1.23–1.73)	2.85 (2.47–3.28)	3.05 (2.65–3.51)	1.35 (1.00–1.83)	5.27 (4.03–6.90)	4.44 (3.48–5.66)
Ketorolac (parenteral)	1.62 (1.29–2.03)	3.15 (2.65–3.75)	3.68 (3.08–4.41)	1.52 (1.03–2.24)	7.01 (4.99–9.86)	5.38 (4.00–7.24)

stroke, in particular ketorolac, with ORs >3. In the sensitivity analysis, we excluded the recent 7 days of drug exposure and found the risk was markedly reduced. These findings suggested that parenteral NSAIDs caused an immediate risk with a hazard period no longer than 7 days. Another possible explanation included that NSAIDs were used for headache caused by intracerebral or subarachnoid hemorrhage (reverse causation), although this may play little role because only 6% patients receiving NSAIDs had symptoms of a headache. Ketorolac was a potent analgesic that was frequently used parenterally for acute pain relief. Several reports suggested an unfavorable risk–benefit ratio for ketorolac use due to a high risk of upper gastrointestinal tract bleeding and acute renal failure.[22–24] However, there was a paucity of population-based data examining its cardiovascular and cerebrovascular safety. We suggested cautious use or even avoidance of ketorolac, especially in populations at risk of stroke, until further studies supporting its rational use in clinical practice.

We observed a higher proportion of patients with stroke having a hypertension diagnosis or receiving a prescription of antihypertensive medication 1 to 30 days before their hospitalization. This correlation between NSAID use and increases in blood pressure before stroke may provide additional insight into the mechanism responsible for their cerebrovascular toxicity. Our study showed celecoxib that had a more favorable hypertensive effect suggested by a meta-analysis of randomized controlled trials was associated with a lower increase in stroke risk as compared with other NSAIDs.[25] In addition, studies showed that coxibs increased the risks of peripheral edema, renal dysfunction, hypertension, and subsequently, increase in cardiovascular events.[26,27] Further studies were required to evaluate whether choice of a drug or a regimen has less effect on blood pressure or close monitoring and treatment of blood pressure rise during NSAID use might reduce cardio- and cerebrovascular risk.

The risk for ischemic stroke associated with nonselective NSAIDs seemed to be attenuated by regular aspirin use. Similar findings were observed by a population-based study of elderly adults showing that current users of naproxen combined with aspirin appeared to have a lower risk for myocardial infarction than those not receiving concomitant aspirin therapy.[28] Another cohort study also suggested regular aspirin use reduced the cardiovascular risk associated with certain selective and nonselective NSAIDs.[29] These findings suggested the derangement in prostaglandin metabolism and imbalance between COX-1 and COX-2 activity by NSAIDs use was inhibited by regular aspirin use. In contrast, the risk for hemorrhagic stroke associated with NSAID use was not further increased among regular aspirin users in our study, probably because most of them took low-dose aspirin.

There were several limitations in our study. First, we identified patients with acute ischemic and hemorrhagic stroke by International Classification of Diseases, 9th Revision, Clinical Modification codes. We could not exclude the possibility that 1 of the diagnoses was incorrectly coded as the other, but this will not substantially change our findings because results were similar between ischemic and hemorrhagic stroke. Second, we did not take over-the-counter NSAID use into account, which would probably cause nondifferential misclassification and thus biased the study results to the null. Third, we did not have information on risk factors such as body mass index, cigarette smoking, and alcohol consumption. However, these lifestyle factors will probably not change substantially during a relatively short study period and thus could be partially controlled by the case–crossover design. Forth, we could not exclude possible time-varying within-subject confoundings such as migraine attack that are associated with disease severity over time or trend in NSAID use. Because only 0.5% of the patients with stroke had a diagnosis of migraine, failure to control it probably did not cause substantial confoundings. The multivariable analysis may also overcontrol some of the intermediate variables responsible for cerebrovascular risk associated with NSAIDs. Finally, this study only assessed risk for short-term use of NSAIDs. Our findings would probably not generalize to the risk associated with long-term use, although no available evidence suggested that cerebrovascular risk associated with NSAID use might change over time.

In conclusion, our study found use of selective and nonselective NSAIDs was associated with a modest but significantly increased risk of both ischemic and hemorrhagic stroke. The strikingly high risk associated with ketorolac use needed to be confirmed in further studies.

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Disclosures

None.

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